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Editorial

Metoprolol Metabolites' Ratios and/or Enantiomeric Profiles: A Simple and Low-Cost Tool for Personalized Medicine through CYP2D6 Phenotyping

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Metoprolol concentrations exhibited very wide variations after oral administration of a given dose in plasma,[1-4] urine,[4-8] exhaled breath condensate[4] and aqueous humor.[2,3] The maximum plasma concentrations of metoprolol after oral administration of 50 mg·day^{-1} for 8 days in young volunteers and elderly hypertensive patients were 83 and 105 mg·L^{-1}. No significant difference was observed in plasma concentration, t_{max}, area under the curve, clearance, half-life, and protein binding among young and elderly groups.[1] Plasma concentrations varied from 52-340 nmol·L^{-1},[2] 25-1030 nmol·L^{-1},[3] and 3.38-187.38 μg·L^{-1}.[4] A recent paper reported a higher dose-adjusted metoprolol concentration in females (N=273) in comparison with the males (N=733), *i.e.* 138.44 mg·L^{-1} versus 101.08 mg·L^{-1} ($p<0.002$) in which the higher concentration of metoprolol in females persists after adjusting for age and daily dose ($p<0.025$) and also for concentration: dose ratio, which was 21% higher in females ($p<0.0002$).[9] This finding is supported by the higher risk of adverse drug reactions in females.[10,11] In an Iranian study, the clearance of another β-blocker, propranolol (1.97 L·kg^{-1}·h^{-1}) was greater than the mean value of other studies (0.96 L·kg^{-1}·h^{-1}) and the half-life (1.98 h) was shorter than the mean of other studies (3.4 h).[12] In another study conducted on brain-injured patients,[13] the total serum concentrations of phenytoin for most of the patients were below the therapeutic range. This finding is in agreement with similar studies conducted on Iranian patients in which the others observed 100%,[14,15] 85%,[16] and 70%[17] of total serum phenytoin concentrations below the therapeutic range. These variations emphasize the effect of genetics on the drug's action. The urinary concentration of metoprolol also varied widely, *i.e.* 18.77-4990.65 μg·L^{-1}.[4] The cumulative urinary excretion of the metabolites after taking 50 mg metoprolol tartrate for 48–72 h varied between 29% to 89 % in renal failure patients, whereas it was approximately 95 % in healthy volunteers.[18] In a study by Chiu *et al.*,[19] 51.4% of the administered dose (100 mg) was changed to metoprolol's main metabolite (α-hydroxymetoprolol) and eliminated via kidney while the unchanged metoprolol was about 8.3 to 62.8% in urine. Yilmaz *et al.*[20] have reported the percentage of unchanged excreted metoprolol within 14 h after oral administration to be about 5.6%. Additionally, Quarterman *et al.*[21] reported a range of 5.6 and 2.8 % (expressed as a % of dose) for the excretion of metoprolol tartrate via kidney, respectively for 18-25 and 63-74 years-old people. Metoprolol concentrations in aqueous humor were 48-247 nmol·L^{-1} [2] and 14-540 nmol·L^{-1}.[3] The exhaled breath condensate concentration was in the range of 1.94-18.95 μg·L^{-1}.[4] Critical review of the analytical methods used for the quantification of metoprolol in biological samples revealed that they are validated methods and the source of variations is related to the individual variations among the patients.

Metoprolol absorption is rapid and complete, however, 40-50 % of the orally administered drug reaches the systemic blood circulation due to the first pass effect.[22] The volume of distribution of metoprolol is 4.2 L·kg^{-1}. About 11% of the administered dose is bound to plasma proteins, mainly to albumin.[23] Metoprolol first-pass hepatic metabolism is mainly driven by the activity of the CYP2D6 enzyme and, to a lesser extent, due to the activity of the CYP3A4 enzyme.[22] Since the CYP2D6 sparteine-debrisoquine polymorphism was first described in the mid-1970s, a significant genetic diversity has been discovered, with nearly 100 different polymorphisms identified. Some of these CYP2D6 polymorphisms completely deactivate the enzyme, while others do not affect its activity. These gene variants give rise to four metabolizer phenotypes used to describe CYP2D6 drug metabolism *in vivo*: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) and ultrarapid metabolizer (UM). Depending on the phenotype, the plasma concentration of metoprolol can vary widely, ranging from subtherapeutic levels in UMs to potentially toxic levels in PMs, thereby increasing the risk of adverse effects such as hypotension and bradycardia.[24] This metabolic pathway is saturable.[25] CYP2D6 is absent in about 8% (PMs) of Caucasians and about 2% of most other populations. Wojtczak *et al.*[26] showed the relationship

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between CYP2D6 genotype and plasma concentration of metoprolol in patients with ischemic heart disease. They reported the mean of the steady-state concentration of metoprolol of 96.81 ± 40.04 (range of 10.68 to 143.55) $mg{\cdot}L^{-1}$ for all patients (100%), 92.25 ± 36.78 $mg{\cdot}L^{-1}$ for EMs (94%) and 168.22 ± 5.61 $mg{\cdot}L^{-1}$ for PMs (6%).[26] Previous studies showed that 3-6 times higher metoprolol concentrations could be achieved in PMs in comparison with the EMs after a single dose and with repeated dosing.[27] The elimination of metoprolol is mainly renal and less than 5% of an oral dose is recovered unchanged in the urine. It should be noted that the systemic availability and half-life of metoprolol are not noticeably different between individuals with renal failure and healthy individuals, and the half-life is reported to be 3–4 h on average.[23,28] Nearly 85% of metoprolol metabolites are excreted in urine along with a small fraction of unchanged drug, making urine an ideal biological sample for pharmacokinetic and therapeutic drug monitoring investigations.[25] The half-life of metoprolol in hypertensive patients was also reported to be within the range of 2.2 to 6.2 hours.[29] In addition to the changes in pharmacokinetic parameters of metoprolol, there is some evidence that reveals the effect of prolonged administration of metoprolol on gut microbiota[25] which is considered as a possible cause of hypertention.[30]

Patients' metabolizing rate, age, and gender could alter metoprolol concentration in biological fluids.[9,28] The aforementioned reports revealed that metabolism of metoprolol plays the most affecting role in the levels of the drug in biological fluids. As noted above, CYP2D6 is the main enzyme that metabolizes metoprolol. Genetic variants are the most important factor in justifying individual differences in drug efficacy and safety.[31] To date, about 400 pharmacogenomic variants have been included in FDA labels.[32] Genotyping is the most common procedure to be used which is a costly[33] and is not feasible in low income societies. Kouhi *et al.*[34] reported the frequency of five CYP2D6 alleles in the Azeri population by genotyping 100 healthy volunteers and found that 63% of the cases had EM or UM phenotypes. In our recent study,[4] 57% of the patients showed a plasma concentration of < 60 $mg{\cdot}L^{-1}$ which is justified by the pharmacogenetic results of the Azeri population.[34] This findings confirmed our results on phenytoin concentrations in the pilot study conducted on Azeri patients.[13]

Different metabolic rates result in various concentration ratios of the parent drug and its metabolites, and this could be used to classify patients according to their metabolic rates. Brocker *et al.*[25] Showed that metoprolol to demethylmetoprolol and metoprolol to hydroxylmetoprolol ratios in urine are closely correlated with CYP2D6 activity. They concluded that the metabolites could be used to estimate the CYP2D6 genotype independent of the dose or time after drug intake.[25] Sohn *et al.*[35] proposed a similar procedure using metoprolol plasma and/or metoprolol to hydroxylmetoprolol ratios. They tested their proposal on Korean and Japanese patients and found that the ratios were 103.7 and 147.0 for PMs in Korean and Japanese patients, respectively, and the corresponding ratios were 0.8 and 0.9 for EMs.[35] On the other hand, metoprolol demonstrates stereoselective metabolism that is reliant on the oxidation phenotype, and patients could be classified as poor or extensive metabolizers. It has been shown that the S/R enantiomeric ratio of metoprolol in PMs was 1.1, whereas the ratio for EMs was 1.7.[36] The S/R ratios in another study were 1.6, 1.3, and 1.0, respectively, for patients with genotypes of two, one, and zero functional alleles.[27] It is worth noting that the determination of metoprolol and its metabolites and also their enantiomers is a simpler and cheaper procedure for classifying patients into PM, IM, EM and UM metabolizer groups, in comparison to the genotyping procedure. Using this simple method, especially in routin use, could provide a low cost method for more precise dose adjustment of metoprolol and other drugs metabolized by CYP2D6 enzyme. Concering the effects of patients' phenotype, age and gender better drug regimen could be provided.

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Author Contributions

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Conflict of Interest

There is no conflict of interest.

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